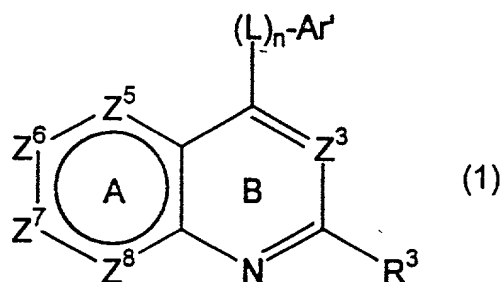


Claims

1. A method to treat conditions characterized by enhanced p38- $\alpha$  activity and/or enhanced TGF- $\beta$  activity, which method comprises administering to a subject in need of such treatment a compound of the formula:



or the pharmaceutically acceptable salts thereof

wherein  $R^3$  is a noninterfering substituent;

each Z is  $CR^2$  or N, wherein no more than two Z positions in ring A are N, and

wherein two adjacent Z positions in ring A cannot be N;

each  $R^2$  is independently a noninterfering substituent;

L is a linker;

n is 0 or 1; and

$Ar'$  is the residue of a cyclic aliphatic, cyclic heteroaliphatic, aromatic or heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents.

2. The method of claim 1 wherein said condition is a proinflammation response or a fibroproliferative response or both.

3. The method of claim 2 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory

disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, or pyresis.

4. The method of claim 2 wherein said fibroproliferative response is associated with a renal disorder, a vascular disorder, a fibrosis, an autoimmune disorder, an eye disease, excessive scarring, a neurological condition, myelofibrosis, tissue thickening, nasal polyposis, a polyp, liver cirrhosis, or osteoporosis.

5. The method of claim 4 wherein said renal disorder, is glomerulonephritis, diabetic nephropathy, renal interstitial fibrosis, renal fibrosis in transplant patients receiving cyclosporin, and HIV-associated nephropathy; and wherein said vascular disorder is progressive systemic sclerosis, polymyositis, scleroderma, dermatomyositis, eosinophilic fascitis, morphea, or Raynaud's syndrome; and wherein said fibrosis is associated with adult respiratory distress syndrome, idiopathic pulmonary fibrosis, interstitial pulmonary fibrosis, cardiac fibrosis, keloid formation, or hypertrophic scarring; and wherein said autoimmune disorder is systemic lupus erythematosus, scleroderma, or rheumatoid arthritis; and wherein said eye disease is retinal detachment, cataracts, or glaucoma; and wherein said neurological condition is CNS injury, Alzheimer's disease, or Parkinson's disease.

6. The method of claim 1 wherein  $R^3$  is a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N.

7. The method of claim 6 wherein  $R^3$  is alkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each unsubstituted or substituted with 1-3 substituents.

8. The method of claim 7 wherein said substituents are independently selected from the group consisting of halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C) and with respect to any aryl or heteroaryl moiety, said group further including alkyl (1-6C).

9. The method of claim 1 wherein said substituents on substituted Ar' are independently selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C),

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C).

10. The method of claim 9 wherein Ar' is phenyl, 2-, 3-, or 4-pyridyl, 2- or 4-pyrimidyl, indolyl, isoquinolyl, quinolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzofuranyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, or morpholinyl, all of which may optionally be substituted.

11. The method of claim 1 wherein each R<sup>2</sup> is independently a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N.

12. The method of claim 11 wherein each R<sup>2</sup> is independently H, alkyl, alkenyl, alkynyl, acyl or hetero-forms thereof or is aryl, arylalkyl, heteroalkyl, heteroaryl, or

heteroarylalkyl, each unsubstituted or substituted with 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R,

5. -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C),

and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl

10. (1-4C), or

R<sub>2</sub> is selected from the group consisting of halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, NRSOR, NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, NRSOR, NRSO<sub>2</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C).

15.

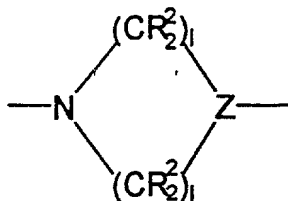
13. The method of claim 11 wherein said substituents on R<sup>2</sup> are independently selected from the group consisting of R<sup>4</sup>, halo, OR<sup>4</sup>, NR<sup>4</sup>, SR<sup>4</sup>, -OOCR<sup>4</sup>, -NROCR<sup>4</sup>, -COOR<sup>4</sup>, R<sup>4</sup>CO, -CONR<sup>4</sup>, -SO<sub>2</sub>NR<sup>4</sup>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R<sup>4</sup> is independently H, or optionally substituted alkyl (1-6C), or optionally substituted arylalkyl (7-12C) and wherein two R<sup>4</sup> or two substituents on said alkyl or arylalkyl taken together may form a fused aliphatic ring of 5-7 members.

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14. The method of claim 1 wherein n is 0 or n is 1 and L is a bivalent residue that provides a distance of 2-8Å between ring B and Ar'.

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15. The method of claim 14 wherein L is S(CR<sup>2</sup>)<sub>m</sub>, -NR<sup>1</sup>SO<sub>2</sub>(CR<sup>2</sup>)<sub>l</sub>, SO<sub>2</sub>(CR<sup>2</sup>)<sub>m</sub>, SO<sub>2</sub>NR<sup>1</sup>(CR<sup>2</sup>)<sub>l</sub>, NR<sup>3</sup>(CR<sup>2</sup>)<sub>m</sub>, NR<sup>1</sup>CO(CR<sup>2</sup>)<sub>l</sub>, O(CR<sup>2</sup>)<sub>m</sub>, or OCO(CR<sup>2</sup>)<sub>l</sub>.



wherein Z is N or CH and wherein m is 0-4 and l is 0-3;

R<sup>1</sup> is H, alkyl or arylalkyl where the aryl moiety may be substituted by 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C);

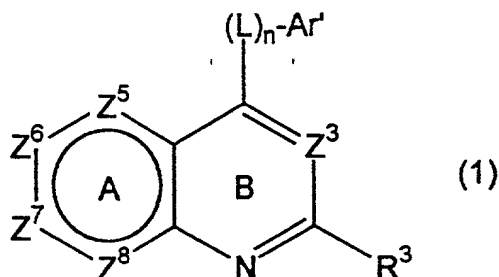
and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR<sub>2</sub>, SR, -SOR, -SO<sub>2</sub>R, -OCOR, -NRCOR, -NRCONR<sub>2</sub>, -NRCOOR, -NRSOR, -NRSO<sub>2</sub>R, -OCONR<sub>2</sub>, RCO, -COOR, -SO<sub>3</sub>R, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or alkyl (1-4C); and

R<sup>2</sup> is as defined in claim 12.

16. The method of claim 1 wherein the compound of formula (1) is selected from the group consisting of compounds 1-87 herein.

17. The method of claim 1 wherein the compound of formula (1) is selected from the group consisting of compounds shown in Figures 1A-1C herein.

18. A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity and/or enhanced TGF-β activity which composition comprises a therapeutically effective amount of a compound of the formula



or the pharmaceutically acceptable salts thereof

wherein  $R^3$  is a noninterfering substituent;

each Z is  $CR^2$  or N, wherein no more than two Z positions in ring A are N, and

5 wherein two adjacent Z positions in ring A cannot be N;

each  $R^2$  is independently a noninterfering substituent;

L is a linker;

n is 0 or 1; and

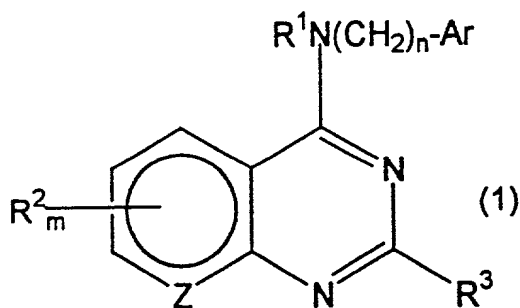
10  $Ar'$  is the residue of a cyclic aliphatic, cyclic heteroaliphatic, aromatic or heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents in admixture with at least one pharmaceutically acceptable excipient.

19. The composition of claim 18 which further contains an additional therapeutic agent.

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20. The composition of claim 19 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

21. A compound of the formula:



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and the pharmaceutically acceptable salts thereof

wherein each  $R^2$  is independently a noninterfering substituent;

m is an integer of 0-4;

Z is CH;

5  $R^1$  is alkyl (1-6C) or arylalkyl optionally substituted on the aryl group with 1-3 substituents independently selected from alkyl (1-6C), halo, OR,  $NR_2$ , SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C);

n is 0, 1 or 2; and

10 (a) Ar is phenyl, substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR,  $NR_2$ , SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C), or pyridyl, indolyl, or pyrimidyl, each optionally substituted with at least one group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR,  $NR_2$ , SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); and

15  $R^3$  is a branched or cyclic alkyl group (5-7C) or is phenyl optionally substituted with 1-2 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR,  $NR_2$ , SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); or

20 (b) Ar is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR,  $NR_2$ , SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub>, CN, CF<sub>3</sub>, and NO<sub>2</sub>, wherein each R is independently H or lower alkyl (1-4C); and

25  $R^3$  is a branched or cyclic alkyl group (5-7C) or is phenyl substituted with 1-2 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, -SO<sub>2</sub>NR<sub>2</sub>, CN, and CF<sub>3</sub>, wherein each R is independently H or lower alkyl (1-4C); or

(c) Ar is phenyl substituted with a group selected from the group consisting of optionally substituted  $\text{NR}_2$ , SR, -NROCR, RCO, -CONR<sub>2</sub>,  $\text{SO}_2\text{NR}_2$ , CN, and  $\text{CF}_3$ , wherein each R is independently H or lower alkyl (1-4C); or pyridyl substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR,  $\text{NR}_2$ , SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>,  $\text{SO}_2\text{NR}_2$ , CN,  $\text{CF}_3$ , and  $\text{NO}_2$ , wherein each R is independently H or lower alkyl (1-4C); or indolyl or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR,  $\text{NR}_2$ , SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>,  $\text{SO}_2\text{NR}_2$ , CN,  $\text{CF}_3$ , and  $\text{NO}_2$ , wherein each R is independently H or lower alkyl (1-4C); and

$\text{R}^3$  is a branched or cyclic alkyl group (5-7C) or is phenyl optionally substituted with 1-2 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR,  $\text{NR}_2$ , SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, - $\text{SO}_2\text{NR}_2$ , CN,  $\text{CF}_3$ , and  $\text{NO}_2$ , wherein each R is independently H or lower alkyl (1-4C); or

(d) Ar is phenyl, pyridyl, indolyl, or pyrimidyl, each optionally substituted with a group selected from the group consisting of optionally substituted alkyl (1-6C), halo, OR,  $\text{NR}_2$ , SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>,  $\text{SO}_2\text{NR}_2$ , CN,  $\text{CF}_3$ , and  $\text{NO}_2$ , wherein each R is independently H or lower alkyl (1-4C); and

$\text{R}^3$  is a branched or cyclic alkyl group (5-7C) or is phenyl substituted with 1-2 substituents which substituents are selected from the group consisting of alkyl (1-6C), halo, OR, SR, -OOCR, -NROCR, RCO, -COOR, -CONR<sub>2</sub>, - $\text{SO}_2\text{NR}_2$ , CN,  $\text{CF}_3$ , and  $\text{NO}_2$ , wherein each R is independently H or lower alkyl (1-4C).

22. The compound of claim 1 which is selected from the group consisting of 2-phenyl-4-(4-pyridylamino)-quinazoline;

2-(2-bromophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-chlorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-fluorophenyl)-4-(4-pyridylamino)-quinazoline;

2-(2-methylphenyl)-4-(4-pyridylamino)-quinazoline;

2-(4-fluorophenyl)-4-(4-pyridylamino)-quinazoline;



2-(3-methoxyanilyl)-4-(4-pyridylamino)-quinazoline;  
2-(2,6-dichlorophenyl)-4-(4-pyridylamino)-quinazoline;  
2-(2,6-dibromophenyl)-4-(4-pyridylamino)-quinazoline;  
2-(2,6-difluorophenyl)-4-(4-pyridylamino)-quinazoline;  
5 2-(2-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;  
2-(4-fluorophenyl)-4-(4-pyridylamino)-6, 7-dimethoxyquinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-nitroquinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-aminoquinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-7-aminoquinazoline;  
10 2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(3-methoxybenzylamino)-quinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methoxybenzylamino)-quinazoline;  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(2-isobutylamino)-quinazoline; and  
2-(2-fluorophenyl)-4-(4-pyridylamino)-6-(4-methylmercaptobenzylamino)-  
quinazoline.